

REMARKS

Claims 1-14 and 29-40 are pending in this application. Claims 1, 2, 13, 14, 29, 32, 36, 39 and 40 have been amended. It is respectfully requested that claims 41-45 be entered into this application.

In claim 1, the group $N(C(O)CF_3)$ as a definition of Z has been corrected.

The Examiner has objected to claims 2, 13, 14, and 29 and has rejected claims 1-14 and 29-40 under 35 USC 112, second paragraph. Applicants respectfully traverse these objections and rejections.

Claim 2 has been amended to correct the case of $SO_2NH(C_1-C_6 \text{ alkyl})$.

Claim 13 has been amended to insert a comma between neurogenerative diseases and gastrointestinal diseases. Claim 13 has also been amended to delete “such as fibromyalgia” and “including cerebral ischemia” and to add excitotoxic neuronal damage. Support for this is found on page 26, line 7.

New claim 41 depends from claim 13 and defines the pain perception as fibromyalgia.

New claim 42 depends from claim 13 and defines the ischemic neuronal damage as cerebral ischemia.

Claim 14 has been amended to delete the phrase “such as depression and postpartum depression”. New claim 43 is presented to include this subject matter. Claim 14 has been amended to delete “including a human”. This is the subject matter of new claim 45.

Claim 29 has been amended to correct the subscripts in R_{24} and R_{25} .

Claim 32 has been amended to insert - - and - - between “depression” and “child”.

Claim 36 has been amended to delete the word “including”.

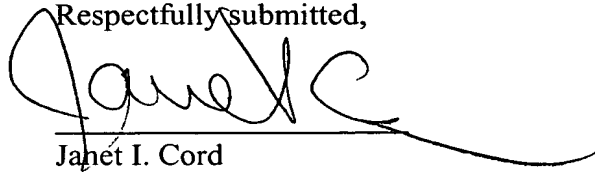
Claim 39 has been amended to depend from claim 44. Claim 44 depends from claim 14 and defines the ischemic neuronal damages as cerebral ischemia.

Claim 40 has been amended to add a period at the end of the claim.

Accordingly it is respectfully requested that the objection to the claims and the rejection of the claims be withdrawn.

It is submitted that the present application is in condition for allowance and favorable consideration is respectfully requested.

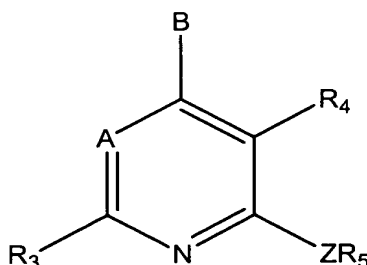
Respectfully submitted,

A handwritten signature in black ink, appearing to read 'Janet I. Cord', with a long, sweeping horizontal line extending to the right.

Janet I. Cord
c/o Ladas & Parry
26 West 61st Street
New York, NY 10023
Telephone No. 212-708-1935
Registration No. 33,758

MARKED-UP COPY

Claim 1 (Twice Amended). A compound of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is N;

B is $-\text{NR}_1\text{R}_2$, $-\text{CR}_1\text{R}_2\text{R}_{11}$, $-\text{C}(=\text{CR}_2\text{R}_{12})\text{R}_1$, $-\text{NHCHR}_1\text{R}_2$, $-\text{OCHR}_1\text{R}_2$, $-\text{SCHR}_1\text{R}_2$, $-\text{CHR}_2\text{OR}_1$, $-\text{CHR}_1\text{OR}_2$, $-\text{CHR}_2\text{SR}_1$, $-\text{C}(\text{S})\text{R}_2$, $-\text{C}(\text{O})\text{R}_2$, $-\text{CHR}_2\text{NR}_1\text{R}[2]_2$, $-\text{CHR}_1\text{NHR}_2$, $-\text{CHR}_1\text{N}(\text{CH}_3)\text{R}_2$, or $-\text{NR}_{12}\text{NR}_1\text{R}_2$;

Z is NH, O, S, $-\text{N}(\text{C}_1\text{-C}_2 \text{ alkyl})-$, $[-\text{NC}(\text{O})\text{CF}_3] \text{N}(\text{C}(\text{O})\text{CF}_3)_2-$ or $-\text{C}(\text{R}_{13}\text{R}_{14})-$, wherein R_{13} and R_{14} are each, independently, hydrogen, trifluoromethyl or methyl, or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl, or $-\text{C}(\text{R}_{13}\text{R}_{14})$ is a cyclopropyl group, or Z is nitrogen or CH and forms a five or six membered heterocyclic ring fused with R_5 , which ring optionally comprises two or three further hetero members selected independently from oxygen, nitrogen, NR_{12} , and $\text{S}(\text{O})_m$, and optionally comprises from one to three double bonds, and is optionally substituted with halo, $\text{C}_1\text{-C}_4$ alkyl, $-\text{O}(\text{C}_1\text{-C}_4 \text{ alkyl})$, NH_2 , NHCH_3 , $\text{N}(\text{CH}_3)_2$, CF_3 , or OCF_3 , with the proviso that said ring does not contain any $-\text{S-S}-$, $-\text{S-O}-$, $-\text{N-S}-$, or $-\text{O-O}-$ bonds, and does not comprise more than two oxygen or $\text{S}(\text{O})_m$ heterologous members;

R_1 is $\text{C}(\text{O})\text{H}$, $\text{C}(\text{O})(\text{C}_1\text{-C}_6 \text{ hydrocarbyl})$, $\text{C}(\text{O})(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl})$, $\text{C}(\text{O})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl})$, $\text{C}(\text{O})(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})(\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl})$, $-\text{C}(\text{O})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene})(\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl})$, $\text{C}_1\text{-C}_6 \text{ hydrocarbyl}$, $\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl}$, $\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl}$, $-(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl})$, $\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene}(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl})$, $-(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})(\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl})$, $-(\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene})(\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl})$, or $-\text{O-aryl}$, or $-\text{O}-(\text{C}_1\text{-C}_6 \text{ hydrocarbylene})\text{-aryl}$; wherein said aryl, $\text{C}_4\text{-C}_8 \text{ heterocyclohydrocarbyl}$, $\text{C}_1\text{-C}_6 \text{ hydrocarbyl}$, $\text{C}_3\text{-C}_8 \text{ cyclohydrocarbyl}$, $\text{C}_3\text{-C}_8 \text{ cyclohydrocarbylene}$, and $\text{C}_1\text{-C}_6$

hydrocarbylene groups may each independently be optionally substituted with from one to six fluoro and may each independently be optionally substituted with one or two substituents R_8 independently selected from the group consisting of C_1 - C_4 hydrocarbyl, $-C_3$ - C_8 cyclohydrocarbyl, hydroxy, chloro, bromo, iodo, CF_3 , $-O$ -(C_1 - C_6 hydrocarbyl), $-O$ -(C_3 - C_5 cyclohydrocarbyl), $-O$ -CO-(C_1 - C_4 hydrocarbyl), $-O$ -CO-NH(C_1 - C_4 hydrocarbyl), $-O$ -CO-N(R_{24})(R_{25}), $-N$ (R_{24})(R_{25}), $-S$ (C_1 - C_4 hydrocarbyl), $-S$ (C_3 - C_5 cyclohydrocarbyl)-N(C_1 - C_4 hydrocarbyl)CO(C_1 - C_4 hydrocarbyl), $-NH$ CO(C_1 - C_4 hydrocarbyl), $-COO$ (C_1 - C_4 hydrocarbyl), $-CONH$ (C_1 - C_4 hydrocarbyl), $-CONC_1$ - C_4 hydrocarbyl)(C_1 - C_2 hydrocarbyl), CN , NO_2 , $-OSO_2$ (C_1 - C_4 hydrocarbyl), S^+ (C_1 - C_6 hydrocarbyl)(C_1 - C_2 hydrocarbyl), $-SO$ (C_1 - C_4 hydrocarbyl) and $-SO_2$ (C_1 - C_4 hydrocarbyl); and wherein the C_1 - C_6 hydrocarbyl, C_1 - C_6 hydrocarbylene, C_5 - C_8 cyclohydrocarbyl, C_5 - C_8 cyclohydrocarbylene, and C_5 - C_8 heterocyclohydrocarbyl moieties of R_1 may optionally independently contain from one to three double or triple bonds; and wherein the C_1 - C_4 hydrocarbyl moieties and C_1 - C_6 hydrocarbyl moieties of R_8 can optionally independently be substituted with hydroxy, amino, C_1 - C_4 alkyl, aryl, $-CH_2$ -aryl, C_3 - C_5 cycloalkyl, or $-O$ -(C_1 - C_4 alkyl), and can optionally independently be substituted with from one to six fluoro, and can optionally contain one or two double or triple bonds; and wherein each heterocyclohydrocarbyl group of R_1 contains from one to three heteromoieties selected from oxygen, $S(O)_m$, nitrogen, and NR_{12} ;

R_2 is hydrogen, C_1 - C_{12} hydrocarbyl, C_3 - C_8 cyclohydrocarbyl, C_4 - C_8 heterocyclohydrocarbyl, $-(C_1$ - C_6 hydrocarbylene)(C_3 - C_8 cyclohydrocarbyl), $-(C_3$ - C_8 cyclohydrocarbylene)(C_3 - C_8 cyclohydrocarbyl), $-(C_1$ - C_6 hydrocarbylene)(C_4 - C_8 heterocyclohydrocarbyl), $-(C_3$ - C_6 cyclohydrocarbylene)(C_4 - C_8 heterocyclohydrocarbyl), aryl, $-(C_1$ - C_6 hydrocarbylene)aryl, or $-(C_3$ - C_8 cyclohydrocarbylene)(aryl); wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro, and C_1 - C_6 alkyl, wherein one of said one to three substituents can further be selected from bromo, iodo, C_1 - C_6 alkoxy, $-OH$, $-O$ -CO-(C_1 - C_6 alkyl), $-O$ -CO-N(C_1 - C_4 alkyl)(C_1 - C_2 alkyl), $-S$ (C_1 - C_6 alkyl), $-S(O)$ (C_1 - C_6 alkyl), $-S(O)_2$ (C_1 - C_6 alkyl), S^+ (C_1 - C_6 alkyl)(C_1 - C_2 alkyl)I', CN , and NO_2 ; and wherein the C_1 - C_{12} hydrocarbyl, $-(C_1$ - C_6 hydrocarbylene), and cyclohydrocarbyl groups of 5 - 8 carbon atoms, cyclohydrocarbylene groups of 5 to 8 carbon atoms and heterocyclohydrocarbyl groups of 5 to 8 atoms of R_2 may optionally independently contain from one to three double or triple bonds; and wherein each heterocyclohydrocarbyl group of R_2 contains from one to three heteromoieties selected from oxygen, $S(O)_m$, nitrogen, and NR_{12} ;

or when R_1 and R_2 are as in $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_1R_2$ or $-NR_1R_2$,

R₁ and R₂ of B may form a saturated 5- to 8-membered ring which may optionally contain one or two double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen, S(O)_m, nitrogen or NR₁₂; and which carbocyclic ring can optionally be substituted with from 1 to 3 substituents selected from the group consisting of hydroxy, C₁-C₄ alkyl, fluoro, chloro, bromo, iodo, CF₃, -O-(C₁-C₄ alkyl), -O-CO-(C₁-C₄ alkyl), -O-CO-NH(C₁-C₄ alkyl), -O-CO-N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -NH(C₁-C₄ alkyl), -N(C₁-C₂ alkyl)(C₁-C₄ alkyl), -S(C₁-C₄ alkyl), -N(C₁-C₄ alkyl)CO(C₁-C₄ alkyl), -NHCO(C₁-C₄ alkyl), -COO(C₁-C₄ alkyl), -CONH(C₁-C₄ alkyl), -CON(C₁-C₄ alkyl)(C₁-C₂ alkyl), CN, NO₂, -OSO₂(C₁-C₄ alkyl), -SO(C₁-C₄ alkyl), and -SO(C₁-C₄ alkyl), wherein one of said one to three substituents can further be selected from phenyl;

R₃ is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, NH₂, NH(C₁-C₂ alkyl), N(CH₃)₂, -NHCOCF₃, -NHCH₂CF₃, S(O)_m(C₁-C₄ alkyl), CONH₂, -CONHCH₃, CON(CH₃)₂, -CF₃, or CH₂OCH₃;

R₄ is hydrogen, C₁-C₄ hydrocarbyl, C₃-C₅ cycloalkyl, -(C₁-C₄ hydrocarbylene)(C₃-C₅ cycloalkyl), -(C₃-C₅ cycloalkylene)(C₃-C₆ cycloalkyl), cyano, fluoro, chloro, bromo, iodo, -OR₂₄, C₁-C₆ alkoxy, -O- cycloalkyl, -O-(C₁-C₄ hydrocarbylene)(C₃-C₅ cycloalkyl), -O-(C₃-C₅ cycloalkylene)(C₃-C₅ cycloalkyl), -CH₂SC(S)O(C₁-C₄ alkyl), CH₂OCF₃, CF₃, amino, nitro, -NR₂₄R₂₅, -(C₁-C₄ hydrocarbylene)-OR₂₄, -(C₁-C₄ hydrocarbylene)Cl, -(C₁-C₄ hydrocarbylene)NR₂₄R₂₅, -NHCOR₂₄, -NHCONR₂₄R₂₅, -CH=NOR₂₄, -NHNOR₂₄R₂₅, -S(O)_mR₂₄, -C(O)R₂₄, -OC(O)R₂₄, -C(O)CN, -C(O)NR₂₄R₂₅, -C(O)NHNOR₂₄R₂₅, and -COOR₂₄, wherein the hydrocarbyl and hydrocarbylene groups of R₄ may optionally independently contain one or two double or triple bonds and may optionally independently be substituted with one or two substituents R₁₀ independently selected from hydroxy, amino, -NHCOCH₃, -NHCOCH₂Cl, -NH(C₁-C₂ alkyl), -N(C₁-C₂ alkyl)(C₁-C₂ alkyl), -COO(C₁-C₄ alkyl), -COOH, -CO(C₁-C₄ alkyl), C₁-C₆ alkoxy, C₁-C₃ thioalkyl, cyano and nitro, and with one to four substituents independently selected from fluoro and chloro;

R₅ is aryl or heteroaryl and is substituted with from one to four substituents R₂₇ independently selected from halo, C₁-C₁₀ hydrocarbyl, -(C₁-C₄ hydrocarbylene)(C₃-C₈ cycloalkyl), -(C₁-C₄ hydrocarbylene)(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkyl), -(C₄-C₈ heterocycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₄-C₈ heterocycloalkyl), C₁-C₄ haloalkyl, C₁-C₄ haloalkoxy, nitro, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, -NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, -CON(OR₂₂)R₂₃, -CO₂R₂₆, -C=N(OR₂₂)R₂₃, and -S(O)_mR₂₃; wherein said C₁-C₁₀ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ hydrocarbylene), (C₃-C₈ cycloalkyl), (C₃-C₈ cycloalkylene), and (C₄-C₈ heterocycloalkyl) groups can be optionally

substituted with from one to three substituents independently selected from C₁-C₄ alkyl, C₃-C₈ cycloalkyl, (C₁-C₄ hydrocarbylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, hydroxy, C₁-C₆ alkoxy, nitro, halo, cyano, -NR₂₄R₂₅, -NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₂)R₂₅, and -S(O)_mR₂₃; and wherein two adjacent substituents of the R₅ group can optionally form a 5-7 membered ring, saturated or unsaturated, fused to R₅, which ring optionally can contain one, two, or three heterologous members independently selected from O, S(O)_m, and N, but not any -S-S-, -O-O-, -S-O-, or -N-S- bonds, and which ring is optionally substituted with C₁-C₄ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), C₁-C₄ haloalkyl, nitro, halo, cyano, -NR₂₄R₂₅, NR₂₄COR₂₅, NR₂₄CO₂R₂₆, -COR₂₄, -OR₂₅, -CONR₂₄R₂₅, CO₂R₂₆, -CO(NOR₂₆)R₂₅, or -S(O)_mR₂₃; wherein one of said one to four optional substituents R₂₇, can further be selected from -SO₂NH(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), SO₂NH(C₃-C₈ cycloalkyl), -SO₂NH(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -NHSO₂(C₃-C₈ cycloalkyl), -NHSO₂(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), and -NHSO₂(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl); and wherein the hydrocarbyl, and hydrocarbylene groups of R₅ may independently optionally contain one double or triple bond;

R₆ is hydrogen, C₁-C₆ alkyl, C₃-C₈ cycloalkyl, -(C₁-C₆ alkylene)(C₃-C₈ cycloalkyl), or -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), wherein said alkyl and cycloalkyl may optionally be substituted with one hydroxy, methoxy, ethoxy or fluoro group;

or R₆ and R₄ can together form an oxo (=O) group, or can be connected to form a 3-8 membered carbocyclic ring, optionally containing one to three double bonds, and optionally containing one, two, or three heterologous ring members selected from O, SO_m, N, and NR₁₂, but not containing any -O-O-, -S-O-, -S-S-, or -N-S- bonds, and further optionally substituted with C₁-C₄ hydrocarbyl or C₃-C₆ cycloalkyl, wherein said C₁-C₄ hydrocarbyl substituent may optionally contain one double or triple bond;

R₁₁ is hydrogen, hydroxy, fluoro, ethoxy, or methoxy;

R₁₂ is hydrogen or C₁-C₄ alkyl;

R₂₂ is independently at each occurrence selected from hydrogen, C₁-C₁₄ alkyl, C₁-C₁₄ haloalkyl, C₃-C₆ alkenyl, C₃-C₆ alkynyl, C₃-C₈ cycloalkyl, (C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), and (C₁-C₄) alkylene)(C₃-C₈ cycloalkyl);

R₂₃ is independently at each occurrence selected from C₁-C₄ alkyl, C₁-C₄ haloalkyl, C₂-C₈ alkoxyalkyl, C₃-C₈ cycloalkyl, -(C₁-C₄ alkylene)(C₃-C₈ cycloalkyl), -(C₃-C₈ cycloalkylene)(C₃-C₈ cycloalkyl), aryl, -(C₁-C₄ alkylene)aryl, piperidine, pyrrolidine, piperazine, N-methylpiperazine, morpholine, and thiomorpholine;

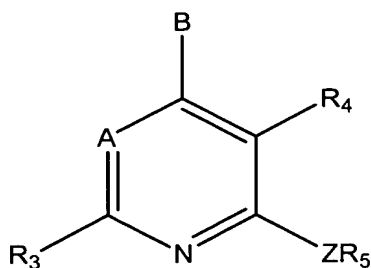
R_{24} and R_{25} are independently at each occurrence selected from hydrogen, $-C_1-C_4$ alkyl, C_1-C_4 haloalkyl, $-(C_1-C_4 \text{ alkylene})OH$, $-(C_1-C_4 \text{ alkylene})-O-(C_1-C_4 \text{ alkyl})$, $-(C_1-C_4 \text{ alkylene})-O-(C_3-C_5 \text{ cycloalkyl})$, C_3-C_8 cycloalkyl, $-(C_1-C_4 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, $-C_4-C_8$ heterocyclohydrocarbyl, $-(C_1-C_4 \text{ alkylene})(C_4-C_8 \text{ heterocyclohydrocarbyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_4-C_8 \text{ heterocyclohydrocarbyl})$, aryl, and $-(C_1-C_4 \text{ alkylene})(\text{aryl})$, wherein the $-C_4-C_8$ heterocyclohydrocarbyl groups can each independently optionally be substituted with aryl, CH_2 -aryl, or C_1-C_4 alkyl, and can optionally contain one or two double or triple bonds; or, when R_{24} and R_{25} are as $NR_{24}R_{25}$, $-C(O)NR_{24}R_{25}$, $-(C_1-C_4 \text{ alkylene})NR_{24}R_{25}$, or $-NHCONR_{24}R_{25}$, then $NR_{24}R_{25}$ may further optionally form a 4 to 8 membered heterocyclic ring optionally containing one or two further hetero members independently selected from $S(O)_m$, oxygen, nitrogen, and NR_{12} , and optionally containing from one to three double bonds;

R_{26} is independently at each occurrence selected from C_1-C_4 alkyl, C_1-C_4 haloalkyl, C_3-C_8 cycloalkyl, $-(C_1-C_4 \text{ alkylene})(C_3-C_8 \text{ cycloalkyl})$, $-(C_3-C_8 \text{ cycloalkylene})(C_3-C_8 \text{ cycloalkyl})$, aryl, and $-(C_1-C_4 \text{ alkylene})(\text{aryl})$; and

wherein each m is independently zero, one, or two,

with the proviso that heterocyclohydrocarbylene groups of the compound of formula I, do not comprise any $-S-S-$, $-S-O-$, $-N-S-$, or $-O-O-$ bonds, and do not comprise more than two oxygen or $S(O)_m$ heterologous members.

Claim 2 (Twice Amended). A compound according to claim 1 of the formula



or a pharmaceutically acceptable salt thereof, wherein

A is N;

B is $-NR_1R_2$, $-CR_1R_2R_{11}$, $-C(=CR_2R_{12})R_1$, $-NHCHR_1R_2$, $-OCHR_1R_2$, $-SCHR_1R_2$, $-CHR_2OR_{12}$, $-CHR_2SR_{12}$, $-C(S)R_2$ or $-C(O)R_2$;

Z is $-NH$, O, S, $N(C_1-C_2 \text{ alkyl})$ or $C(R_{13}R_{14})$ wherein R_{13} and R_{14} are each independently, hydrogen, trifluoromethyl or methyl or one of R_{13} and R_{14} is cyano and the other is hydrogen or methyl;

R_1 is C_1 - C_6 hydrocarbyl which may optionally be substituted with one or two substituents R_8 independently selected from the group consisting of hydroxy, fluoro, chloro, bromo, iodo, CF_3 , C_1 - C_4 alkoxy, -O-CO-(C_1 - C_4 hydrocarbyl), -O-CO-NH(C_1 - C_4 hydrocarbyl), -O-CO-N(C_1 - C_4 hydrocarbyl)(C_1 - C_2 hydrocarbyl), -NH(C_1 - C_4 hydrocarbyl), -N(C_1 - C_2 alkyl)(C_1 - C_4 hydrocarbyl), -S(C_1 - C_4 alkyl), -N(C_1 - C_4)CO(C_1 - C_4 hydrocarbyl), -NHCO(C_1 - C_4 hydrocarbyl), -COO(C_1 - C_4 hydrocarbyl)hydrocarbyl, -CONH(C_1 - C_4 hydrocarbyl), -CON(C_1 - C_4 hydrocarbyl)(C_1 - C_2 alkyl), CN, NO_2 , -SO(C_1 - C_4 hydrocarbyl) and -SO₂(C_1 - C_4 hydrocarbyl), and wherein said C_1 - C_6 hydrocarbyl and the (C_1 - C_4)hydrocarbyl moieties in the foregoing R_1 groups may optionally contain one carbon-carbon double or triple bond;

R_2 is C_1 - C_{12} hydrocarbyl, aryl or -(C_1 - C_4 hydrocarbylene)aryl wherein said aryl is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, imidazolyl, furanyl, benzofuranyl, benzothiazolyl, isothiazolyl, benzisothiazolyl, benzisoxazolyl, benzimidazolyl, indolyl, or benzoxazolyl; 3- to 8-membered cycloalkyl or -(C_1 - C_6 alkylene)cycloalkyl, wherein one or two of the ring carbons of said cycloalkyl having at least 4 ring members and the cycloalkyl moiety of said -(C_1 - C_6 alkylene)cycloalkyl having at least 4 ring members may optionally be replaced by an oxygen or sulfur atom or by N- R_9 wherein R_9 is hydrogen or C_1 - C_4 alkyl; and wherein each of the foregoing R_2 groups may optionally be substituted with from one to three substituents independently selected from chloro, fluoro and C_1 - C_4 alkyl, or with one substituent selected from bromo, iodo, C_1 - C_6 alkoxy, -O-CO-(C_1 - C_6 alkyl), -O-CO-N(C_1 - C_4 alkyl)(C_1 - C_2 alkyl), -S(C_1 - C_6 alkyl), CN, NO_2 , -SO(C_1 - C_4 alkyl), and -SO₂(C_1 - C_4 alkyl), and wherein said C_1 - C_{12} hydrocarbyl and the C_1 - C_4 hydrocarbylene moiety of said -(C_1 - C_4 hydrocarbylene)aryl may optionally contain one carbon-carbon double or triple bond;

or -NR₁R₂ or -CR₁R₂R₁₁ may form a saturated 5- to 8-membered carbocyclic ring which may optionally contain one or two carbon-carbon double bonds and in which one or two of the ring carbons may optionally be replaced by an oxygen or sulfur atom;

R_3 is methyl, ethyl, fluoro, chloro, bromo, iodo, cyano, methoxy, OCF₃, methylthio, methylsulfonyl, CH₂OH, or CH₂OCH₃;

R_4 is hydrogen, C_1 - C_4 hydrocarbyl, fluoro, chloro, bromo, iodo, C_1 - C_4 alkoxy, trifluoromethoxy, -CH₂OCH₃, -CH₂OCH₂CH₃, -CH₂CH₂OCH₃, -CH₂OF₃, CF₃, amino, nitro, -NH(C_1 - C_4 alkyl), -N(CH₃)₂, -NHCOCH₃, -NHCONHCH₃, -SO_n(C_1 - C_4 hydrocarbyl) wherein n is 0, 1 or 2, cyano, hydroxy, -CO(C_1 - C_4 hydrocarbyl), -CHO, cyano or -COO(C_1 - C_4 alkyl) wherein said C_1 - C_4 hydrocarbyl may optionally contain one double or triple bond and may optionally be substituted with one substituent selected from hydroxy, amino, -NHCOCH₃, -NH(C_1 - C_2 alkyl), -N(C_1 - C_2 alkyl)₂, -COO(C_1 - C_4 alkyl), -CO(C_1 - C_4 alkyl), C_1 - C_3 alkoxy, C_1 - C_3 thioalkyl, fluoro, chloro, cyano and nitro;

R₅ is phenyl, naphthyl, thienyl, benzothienyl, pyridyl, quinolyl, pyrazinyl, pyrimidyl, furanyl, benzofuranyl, benzothiazolyl, or indolyl, wherein each of the above groups R₅ is substituted with from one to three substituents independently selected from fluoro, chloro, C₁-C₆ alkyl, and C₁-C₆ alkoxy, or with one substituent selected from hydroxy, iodo, bromo, formyl, cyano, nitro, trifluoromethyl, amino, -(C₁-C₆ alkyl)O(C₁-C₆)alkyl, -NHCH₃, -N(CH₃)₂, -COOH, -COO(C₁-C₄ alkyl), -CO(C₁-C₄ alkyl), -SO₂NH(C₁-C₄ alkyl), -SO₂N(C₁-C₄ alkyl)(C₁-C₂ alkyl), -SO₂NH₂, -NHSO₂(C₁-C₄ alkyl), -S(C₁-C₆ alkyl) and [-SO₂(C₁-C₆ alkyl)] -SO₂(C₁-C₆ alkyl), and wherein the C₁-C₄ alkyl and C₁-C₆ alkyl moieties of the foregoing R₅ groups may optionally be substituted with one or two fluoro groups or with one substituent selected from hydroxy, amino, methylamino, dimethylamino and acetyl;

R₁₁ is hydrogen, hydroxy, fluoro, or methoxy;

R₁₂ is hydrogen or C₁-C₄ alkyl; and

or a pharmaceutically acceptable salt of such compound.

Claim 13 (Amended). A pharmaceutical composition for the treatment of (a) a disorder or condition the treatment of which can be effected or facilitated by antagonizing CRF or (b) a disorder or condition selected from inflammatory disorders, pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive-compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception [such as fibromyalgia]; mood disorders, mood disorders associated with premenstrual syndrome, and postpartum depression; dysthemia; bipolar disorders; cyclothymia; chronic fatigue syndrome; stress-induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; post operative ileus; ulcer; diarrhea; stress-induced fever; human immunodeficiency virus infections; neurodegenerative diseases, gastrointestinal diseases; eating disorder; hemorrhagic stress; chemical dependencies or addictions; drug or alcohol withdrawal symptoms; stress-induced psychotic episodes; euthyroid sick syndrome; syndrome of inappropriate antidiuretic hormone; obesity; infertility; head trauma; spinal cord trauma; ischemic neuronal damage[,]; excitotoxic neuronal damage; [including cerebral ischemia;] epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; hypertension; tachycardia; congestive heart failure; osteoporosis; premature birth; hypoglycemia, and Syndrome X in a mammal or bird, comprising an amount of a compound according to claim 1 that is effective in the treatment of such disorder or condition, and a pharmaceutically acceptable carrier.

Claim 14 (Twice Amended). A pharmaceutical composition according to claim 13 for

the treatment of a disorder selected from inflammatory disorders; pain, asthma, psoriasis and allergies; generalized anxiety disorder; panic; phobias; obsessive compulsive disorder; post-traumatic stress disorder; sleep disorders induced by stress; pain perception; mood disorders [such as depression,, and postpartum depression]; dysthemia; bipolar disorders; cyclothymia; fatigue syndrome; stress induced headache; cancer; irritable bowel syndrome, Crohn's disease; spastic colon; human immunodeficiency virus (HIV) infections; neurodegenerative diseases; gastrointestinal diseases; eating disorders; chemical dependencies and addictions; obesity; infertility; head traumas; spinal cord trauma; ischemic neuronal damage; excitotoxic neuronal damage; epilepsy; stroke; immune dysfunctions; muscular spasms; urinary incontinence; senile dementia of the Alzheimer's type; multi infarct dementia; amyotrophic lateral sclerosis; and hypoglycemia in a mammal[, including a human].

Claim 29 (Amended). A compound as claimed in claim 1 wherein [R24 and R25] R₂₄ and R₂₅ are selected from- CF_3 , $-\text{CHF}_2$, CF_2CF_3 , and CH_2CF_3 [,].

Claim 32 (Amended). A pharmaceutical composition as claimed in claim 14 for treatment of depression, selected from the group consisting of major depression, single episode depression, recurrent depression, and child abuse induced depression.

Claim 36 (Amended). A pharmaceutical composition as claimed in claim 14 for treatment of [stress induced] immune dysfunctions induced by stress selected from the group consisting of [including] porcine stress syndrome, bovine shipping fever, equine paroxysmal fibrillation, confinement dysfunction in chicken, sheering stress in sheep, and human animal interaction stress in dogs.

Claim 39 (Amended). A pharmaceutical composition as claimed in claim [14] 44 for treatment of cerebral ischemia, selected from the group consisting of cerebral hippocampal ischemia[, excitotoxic neuronal damage].

Claim 40 (Amended). A pharmaceutical composition as claimed in claim 14 for treatment of social phobia, agoraphobia, or specific phobias.